In the subject Office Action, the Examiner rejected claims 22-27 under 35 U.S.C. § 101 and the second paragraph of Section 112 for lack of utility and enablement. The Examiner rejected claims 22 and 27 under the second paragraph of 35 U.S.C. § 112 as being indefinite. Lastly, the Examiner rejected claims 22-27 under 35 U.S.C. § 102 as being anticipated by the Holtzman reference.

Applicants respectfully request that the Examiner consider the following remarks in response to the subject Office Action.

Remarks

I. Rejection of Claims Under 35 U.S.C. § 101 and § 112, First Paragraph - Lack of Utility and Enablement

The Examiner rejected claims 22-27 under both 35 U.S.C. § 101 and the first paragraph of 35 U.S.C. § 112 as being drawn to an invention that lacks utility. Specifically, the Examiner asserts that the claimed invention is not supported by either a specific, substantial and credible asserted utility, or a well-established utility.

Applicants respectfully direct the attention of the Examiner to the declaration of Audrey D. Goddard, Ph.D., attached hereto as Appendix A ("the Goddard Declaration"). Please note that the Goddard Declaration will soon be filed as a 1.132 Declaration in Application Serial No. 09/903,925. The Goddard Declaration makes it clear that skilled artisans recognize a well-established utility for the claimed invention at the time of filing.

Specifically, the Goddard Declaration illustrates the acceptance in the art of gene amplification data as an indicator of cancerous tissue. For example, in paragraph 7, Dr. Goddard specifically asserts her opinion that:

> [a]n at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number . . . as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology.

Goddard Declaration, paragraph 7.

The pending claims are directed to antibodies against proteins encoded by one of the amplified DNA sequences. The specification specifically asserts a utility for these antibodies. See, for example, paragraph 0705, stating that "[a]ntagonists (e.g., antibodies) directed against the proteins encoded by the DNAs tested would be expected to have utility in cancer therapy and as useful diagnostic reagents." Thus, considering the Goddard Declaration and the antibody utility asserted in the application, it is clear that skilled artisans recognize a well-established utility for the claimed invention.

The Examiner indicated that the significance of a difference of 1 or 2 PCR cycles is not clear. The specification indicates that one ΔCt unit corresponds to 1 PCR cycle, or *approximately a 2-fold amplification relative to normal* (see paragraph 0661). Furthermore, as indicated above, the Goddard Declaration indicates that a 2-fold increase in gene copy number is considered both significant and useful (see Goddard Declaration paragraph 7, and above). Thus, the ΔCt data is indicative of relevant gene amplification.

The Examiner further indicates that, even if the data demonstrate a slight increase in copy number of PRO357 nucleic acids in primary tumors, such increase would not be indicative of a use of the encoded polypeptide as a diagnostic agent because cancerous tissue is known to be aneuploid. The Examiner asserts that the data presented in the specification were not corrected for aneuploidy, and that a slight amplification of a gene does not necessarily mean over expression in a cancer tissue, but can merely be an indication that the tissue is aneuploid.

Applicants respectfully disagree with this characterization. The data presented in the specification are from experiments using appropriate controls for aneuploidy (see, for example, paragraph 0698). The applicants used framework mapping to control for aneuploidy and to ensure that the observed ΔCt data represent relevant gene amplification. Thus, the reported data are an indication of relevant gene amplification, and support the conclusion that PRO357, and related proteins and antibodies, can be used as a cancer diagnostic. Furthermore, considering the aneuploidy controls used by the Applicants, a skilled artisan would not be required to undertake undue experimentation to practice the claimed invention.

Considering these remarks, Applicants respectfully assert that the claimed invention has utility and is fully enabled. Accordingly, Applicants request that the Examiner reconsider and withdraw the rejections under § 101 and the first paragraph of § 112.

II. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph - Indefiniteness

The Examiner rejected claims 22 and 27 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner acknowledges that the difference between these two claims is the use of the terms "binds" (claim 22) and "specifically binds" (claim 27). Further, the Examiner asserts that a skilled artisan would be unable to determine the difference in scope between the two claims absent an indication in the specification of the difference between these two terms.

Applicants respectfully traverse this characterization of these two terms. The concept of binding between two molecular entities is well known in a variety of arts, including the antibody art, and is appreciated as including a variety of binding relationships. For example, skilled artisans recognize that two molecular entities can bind to each other in a variety of manners, including relatively weak non-covalent interactions such as van der Waals attractions and hydrogen bonding. These forces allow entities to bind to each other in the sense that the entities are associated as a complex and energy must be applied to disassociate the complex. However, this binding is not specific because it can occur between a variety of entities, depending only on the structure of microenvironments within each entity. Between two proteins, for example, a microenvironment of one protein can interact with a microenvironment of the other protein when the two microenvironments contain residues that can interact with each other via these forces. The complex formed between the two entities is typically only temporary, as only minimal energy input is required to disassociate the complex. Accordingly, while the entities are bound during the interaction, the binding that occurs is not considered specific. Skilled artisans recognize that two proteins, such as an

antibody and an unrelated or modified antigen, can bind non-specifically through these and other types of interactions.

Specific binding, however, is a stronger interaction that occurs between two or more molecular entities. Generally, specific binding is a result of numerous interactions between several microenvironments of the two entities that produces a binding relationship that requires greater energy input to disassociate the complex as compared to the energy needed to disassociate a complex of non-specifically bound entities. This type of binding typically results from a relatively high degree of complementarity between several microenvironments of the entities.

Specific binding between antibodies and antigens, the hallmark of the acquired immune system, is exemplary of these binding relationships. Each individual antibody specifically binds an antigen, giving the antibody the ability to discriminate amongst numerous unrelated antigens in favor of the specific antigen.

The difference between specific binding and other types of binding is readily ascertainable by numerous laboratory techniques. Indeed, skilled artisans are readily aware of various data characteristics that distinguish specific binding from other types of binding. For example, specific binding is a saturable phenomena. That is, as the binding sites of one entity are fully occupied by another entity, no additional binding can occur. Thus, in common laboratory binding assays, such as Enzyme-Linked Immunosorbent Assays (ELISA), a plateau is observed on a binding curve as saturation of binding sites occurs. This effect is either not observed or occurs at much higher concentrations with non-specific binding.

Aware of this clear distinction between these two terms in the art, the Applicants did not believe it necessary to include an explicit definition or differentiation for the terms in the specification. Applicants respectfully assert that the above remarks clearly indicate that skilled artisans can determine the difference in scope between these two terms, and respectfully assert that the rejection of claims 22 and 27 is improper. Accordingly, Applicants request that the Examiner reconsider and withdraw the rejection.

III. Priority Determination

The Examiner asserts that the effective priority date for the subject application is the instant filing date of August 30, 2001 because of the alleged lack of utility and enablement. Applicants respectfully traverse this determination, and direct the Examiner's attention to the arguments made herein and the Goddard Declaration.

Applicants request reconsideration of the determination of priority in view of the submission of evidence showing utility of the claimed invention. Furthermore, Applicants request that a final determination of priority be delayed until after the utility rejection is finally resolved.

IV. Rejection of Claims Under 35 U.S.C. § 102 - Anticipation By Holtzman

The Examiner rejected claims 22-27 under § 102 as being anticipated by U.S. 6,225,085 (Holtzman). Specifically, the Examiner asserts that Holtzman teaches an antibody that binds SEQ ID 2 of Holtzman, which has 98.4% identity to the polypeptide to which the claimed antibodies bind (SEQ ID 69 of the present application).

Applicants respectfully traverse this rejection for at least the following reasons. First, Holtzman does not disclose all limitations of any pending claim, and therefore cannot properly serve as an anticipatory reference under 35 U.S.C. §102. Second, the alignment analysis relied on by the Examiner fails to consider several differences between the two polypeptides. These differences are of the type that will affect three-dimensional structure, which, in turn, will affect the ability of antibodies to bind the polypeptides.

1. Holtzman does not disclose all limitations of any pending claim

To anticipate a claim under § 102, a cited reference must disclose each and every limitation of the claim. Even as characterized by the Examiner, Holtzman only discloses an antibody that binds a polypeptide that has 98.4% identity to the polypeptide to which the claimed antibodies bind. The antibody taught by Holtzman cannot be said to bind the polypeptide shown in SEQ ID 69 of the present application simply because the polypeptides have a certain level of identity. Indeed, as detailed below, several

differences exist between the polypeptides. These differences likely confer different three-dimensional structures onto the polypeptides, which will affect the ability of antibodies to bind the polypeptides, specifically or otherwise.

Because of the differences between the polypeptides, all limitations of independent claim 22 are not satisfied. Claims 23-27 depend from independent claim 22. As a result, all limitations of these claims are also not satisfied by the Holtzman reference. Accordingly, Holtzman cannot properly serve as an anticipatory reference under 35 U.S.C. § 102.

2. Examiner's alignment analysis fails to consider several differences between the polypeptides

The Examiner indicates that the Holtzman polypeptide is 98.4% identical to the polypeptide to which the claimed antibodies bind. As support for this proposition, the Examiner attached an alignment of the two polypeptides to the Office Action (Applicants note that the alignment of the two polypeptides is erroneously labeled and referred to as Attachment B, and is actually presented as Attachment A). To investigate the Holtzman polypeptide in detail, Applicants have conducted an extensive alignment analysis between the polypeptide to which the claimed antibodies bind (SEQ ID 69 of the present application, "DNA 44804") and the Holtzman polypeptide (SEQ ID 2 of Holtzman, "Holtzman"). Applicants respectfully direct the attention of the Examiner to Appendix B, attached hereto, which contains the results of the comparative analysis.

As indicated in the results, numerous differences exist between the two polypeptides. First, Holtzman contains an additional 75 residues not present in the DNA44804 polypeptide ("the gap region"). Several additional differences arise at least in part due to this gap in DNA44804. For example, Holtzman contains five N-glycosylation sites while DNA44804 contains only three (see pages 3 and 4 of Appendix B). Also, several differences exist in the located Leucine Rich Repeats (LRR) present in the polypeptides, including the presence of three LRRs in Holtzman within the gap region (see pages 5 and 6 of Appendix B).

In protein-protein binding interactions, such as binding that occurs between antibody and antigen, the three-dimensional structures of the individual proteins play

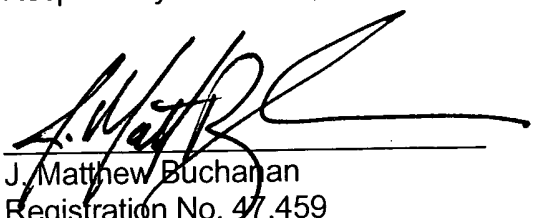
large roles in the binding interactions between the proteins. As is well known in the art, three dimensional structures of proteins are determined in large part by the linear structure of a polypeptide and any post-translational processing, such as glycosylation, that occurs to the protein. Considering the differences detailed above in the linear structures of the proteins (the presence of the gap region in DNA44804, differences in LRRs, etc.) and in the number of glycosylation sites, the Holtzman and DNA44804 polypeptides likely have vastly different three-dimensional structures. For example, the presence of the gap region in DNA44804 represents a deletion of over 10% of the Holtzman protein, which would likely affect folding and ultimate three-dimensional structure. Furthermore, the difference in the number of N-glycosylation sites would result in different quantities of carbohydrate residues being added to the proteins during processing, as well as different location of the carbohydrate residues relative to the ends and center of the polypeptide. This also will affect three-dimensional structure. All of these differences in three-dimensional structures will affect the ability of particular antibodies to bind the two polypeptides.

The comparative test results provided in Appendix B detail many differences that exist between the Holtzman and DNA44804 proteins. As a result, it is clear that the antibody taught by Holtzman does not anticipate the claimed invention. Accordingly, the Holtzman reference is not a proper anticipatory reference of any currently pending claim. The Applicants respectfully request that the Examiner reconsider and withdraw this rejection of the claims.

Applicants believe this reply fully responds to the subject Office Action. If the Examiner believes personal communication would facilitate prosecution of this application, Applicants invite the Examiner to contact their attorney at the number listed below.

Applicants believe no fee is due in connection with the filing of this Reply, however, should any fees be deemed necessary for any reason relating to this paper, the Commissioner is hereby authorized to deduct said fees from Brinks Hofer Gilson & Lione Deposit Account No. 23-1925. A duplicate copy of this document is enclosed.

Respectfully submitted,



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